REMARKS/ARGUMENTS

Claims 33, 56-59, 61 and 63-152 are pending and examined. The claims have not been amended but are reproduced for ease of reference. A supplemental ADS is attached modifying the priority claim. As amended, the application has an effective filing date of May 28, 1999. The priority claim is also amended to designate the present application as a divisional rather than a continuation of its parent. Such is appropriate because the subject matter of the present claims was separated from that of its parent by restriction requirement in the parent case.

All pending claims stand rejected for alleged lack of enablement of the claims under 35 U.S.C. § 112, first paragraph largely for reasons of record.

The application describes a strategy of treating diseases characterized by amyloid deposits of Aβ, such as Alzheimer's disease, using antibodies to Aβ, and shows that levels of Aβ in the brain can be reduced by intravenous administration of the 10D5 antibody in a mouse model. The application also teaches that a similar result can be achieved by using DNA immunization to deliver antibody rather than direct injection of antibody. In applicant's view, given the mature state of molecular genetics, availability of standard vectors and routes of delivery, those in the field would have been able to achieve suitable recombinant expression based on knowledge in the art and teaching in the specification without undue experimentation.

The Examiner disagrees for two main reasons. First, the Examiner alleges that reduction in levels of Aβ shown for 10D5 in the present specification is not predictive of success in treating diseases characterized by amyloid deposits of Aβ disease in view of subsequent results of Bard showing that this antibody does not significantly affect neuritic dystrophy. Second, the Examiner alleges that the field of gene therapy was too unpredictable to obtain suitable recombinant expression.

Many of the Examiner's comments have been addressed in previous responses. Applicant maintains previous remarks without repeating them in full here. Applicant focuses the present response on two new pieces of evidence: (1) a declaration by Dr. J. Steven Jacobsen showing that the 10D5 antibody has beneficial effects on cognitive function, and (2) a declaration by an expert in gene therapy, Dr. David Weiner, regarding the general state of the art, and the feasibility of implementing the claimed methods.

Although Bard reports that the 10D5 antibody does not significantly affect neuritic dystrophy, applicant maintains it reasonable to expect that the antibody does exert some beneficial effect for treatment of diseases characterized by amyloid deposits of Aβ in view of its reduction of brain levels of Aβ peptide, the presumptive primary cause of such diseases. Removal of the primary cause of the disease in an *in vivo* animal model generates an expectation that at least some other aspects of the disease which stem from the primary cause will also be inhibited. This expectation is confirmed by subsequent experiments examining the effect of 10D5 on cognition in a mouse model. The results obtained showed that 10D5 caused a statistically significant improvement in contextual dependent memory in a transgenic mouse model of Alzheimer's disease in comparison with a control treatment.

The above result shows that a reduction in neuritic dystrophy in the assay reported by Bard et al is not a *sine qua non* for treating diseases characterized by amyloid deposits of Aβ. Thus, nothing in Bard is inconsistent with the position that 10D5 or other antibodies that are effective to reduce levels of Aβ in the brain of a mouse model are not effective at least in some respect for treating diseases characterized by amyloid deposits of Aβ. To the contrary, the data provided by Bard support applicant's position that a number of N-terminal antibodies achieving similar results to 10D5 in reducing levels of Aβ in the brain can be readily identified.

The Examiner also discounts Bard on the basis that it is postfiling evidence, and enablement must be shown at the time of filing. Applicant agrees that an application must be enabling as of its effective filing date. However, that enablement is determined from the specification as filed "does not preclude the applicant from providing a declaration after the filing date which demonstrates that the claimed invention works." MPEP 2164.05. Here, postfiling data are being used to confirm that other antibodies capable of reducing levels of Aβ in the brain can be identified in similar fashion to that exemplified in the specification for 10D5.

The Examiner also discounts Bard in that it relates to screening mouse antibodies whereas the present claims refer to chimeric, humanized or human antibodies. In response, the use of chimeric, humanized or human antibodies is expected to reduce immunogenicity of antibodies when used in human. However, there is no reason to think a chimeric or humanized

version of one of the antibodies discussed by Bard, or a human antibody binding to the same epitope, would be significantly less effective than Bard's mouse antibodies.

The Examiner's other main area of disagreement with applicant's position, the allegation that gene therapy is too unpredictable, is addressed in the attached declaration by Dr. Weiner. Dr. Weiner is a founder of the field of gene therapy and has been active in the field for almost twenty years. In Dr. Weiner's opinion, the Examiner has painted an unduly negative picture of gene therapy (Weiner at paragraph (3)). Dr. Weiner's opinion is based in part on the fact that in every year since 1989 numerous human clinical trials have been initiated. As noted by Dr. Weiner, before a drug can enter a human clinical trial, the investigator must submit an application to the FDA or similar body in other countries detailing preclinical work and providing an explanation why the investigation may be successful and this explanation must be found convincing to the FDA before the trial can be allowed to proceed (Id.). The hundreds of approved clinical trials serves as evidence that the FDA or similar bodies in other countries are of the opinion that gene therapy was at least by the mid-1990's sufficiently mature for substantial use in human patients.

Turning to the claimed methods of treatment, Dr. Weiner confirms applicant's previous remarks that delivery of antibody to the blood represents a relatively undemanding form of a gene therapy compared with treatments which require permanent expression of a gene or tissue specific expression (Weiner at paragraph (6)). As such, experimentation is not required to resolve issues relating to tissue specific expression or permantnent expression that have arisen in other forms of gene therapy. Dr. Weiner also confirms that he views the results from a clinical trial involving immunization with Aβ (described in the Koller declaration) as relevant in establishing that event transient low level expression of antibody can be sufficient to have some benefit. (Weiner at paragraph (7)).

Dr. Weiner also confirms that he and others in the field were well familiar with the types of vectors, regulatory systems and methods of delivery used in gene therapy as of 1999 and would not need a patent application to spell out these matters in great details (Weiner at paragraph (8)). Dr. Weiner particularly notes that deleting the E1 gene from adenoviral vectors (as in Arafat's vector) was entirely standard practice as of 1999 (Id.). Dr. Weiner also explains

that it was routine to construct vectors and test expression levels in cell culture before commencing gene therapy (Id.).

Dr. Weiner disagrees with the Examiner that immunogenicity rendered gene therapy in feasible as of 1999. Dr. Weiner says that immunogenicity did not prevent use of adenovirus in numerous clinical trials, and was not a problem using retroviral vectors, adenoassociated virus or naked DNA (paragraph (9)).

Dr. Weiner has also reviewed the Arafat reference, which applicant previously cited as evidence that an antibody could be successfully expressed by a DNA vaccination approach. Dr. Weiner sees nothing of importance in the Arafat reference that was not known in the field of gene therapy by at least 1999 (Weiner at paragraph (10)). Indeed, Dr. Weiner has cited another reference describing similar expression of an antibody from an adenoviral vector at an earlier date, 1997 (Id.).

In sum, Dr. Weiner disagrees with the Examiner's negative view of the field of gene therapy in general, and in particular the extent of problems alleged to exist in carrying out the claimed methods (Weiner at paragraph (11)). In Dr. Weiner's opinion, those in the field including him would have considered it plausible that DNA immunization could be used to deliver an antibody to the blood and achieve similar results for treating Alzheimer's disease to those described in the application when the antibody is directly administered to the blood (Id).

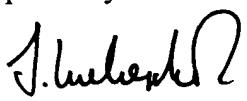
Applicant submits that Dr. Weiner's stature as an expert in the field merits appropriate deference. "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." *Guidelines for Examination of Applications for Compliance with the Utility Requirement* at §B.4. Appropriate deference by an Examiner to the opinion of an expert is also emphasized by *In re Soni*, holding that the opinion of an expert must be accepted "*in the absence of* evidence to the contrary." 34 USPQ2d 1684, 1688 (Fed. Cir. 1995) (emphasis in original). Here, Dr. Weiner has explained why the types of difficulties alleged to exist by the Examiner did not present major hurdles to practicing the claimed methods. As a founder of the field and one who has been active in it for almost twenty years, Dr. Weiner has the knowledge and hands-on experience to

view the types of difficulties alleged to exist by the Examiner in the proper perspective given the state of the art as a whole and the particular nature of the claimed methods.

The above evidence confirms the teaching of the specification that diseases characterized by amyloid deposits of Aβ in the brain can be treated by direct administration of 10D5 or other antibodies to the Aβ1-10 region, and a similar result could have been achieved, without undue experimentation, by using DNA immunization rather than direct administration to deliver antibody to the patient. Withdrawal of the rejection is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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